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EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	PAPER NUMBER
1645	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/674,254	Tabibzadeh
Examiner	**Art Unit**
P rtner	1645

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 27, 2000* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-40* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-40 are pending.

Specification

1. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Incorporation by Reference

2. The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

3. It was also noted that various references are cited at pages 82-90; may citations are incomplete and are not numbered. Reference to subject matter and teaching by the references listed at the end of the specification, by number, such as evidenced at page 58, line 17 "(7-8)," is not clear as NONE of the references have any numbers next to them. How the subject matter referenced at

page 58, for example, corresponds to the list of references at pages 82-90 is confusing. Clarification is requested. No new matter should be added to the specification

Claim Rejections - 35 U.S.C. § 101

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 27-29 are directed to antibodies and markers that are not isolated and purified; the

OR

The claimed invention is directed to non-statutory subject matter.

6. Claims 27-29 and 39 are directed to products of nature that have not been isolated and purified.

Claim Rejections - 35 U.S.C. § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 39 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A genus of peptides that comprise SEQ ID No 3 are claimed but only a single species of protein that comprises SEQ ID No 3 has been described. A single species does not provide a representative number of species for the now claimed genus of peptides of any number of amino acids, and the claimed peptide need not evidence any specific function as set forth in claim 39.

Applicant also broadly describe the invention as embracing proteins and peptides that comprise the amino acid sequence of SEQ ID No 3. The genus of claimed peptide that comprise SEQ ID No is described by a single species of peptide of SEQ ID No 3. Addition proteins that comprise SEQ ID No 3, other than ebaf of the instant specification have not been described by any specific sequence. The written description provision of 35 U.S.C. 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

The specification does not disclose a genus of splice variants of ebaf that encode or comprise SEQ ID No 3. An isolated peptide consisting of SEQ ID NO:3, and may be claimed based upon the nucleotide sequence that encodes the peptide. The skilled artisan cannot envision all the contemplated nucleotide sequences that encode peptides that comprise SEQ ID No 3, nor all of the peptides that are variants thereof, by the detailed chemical structure.

Therefore conception cannot be not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. In the instant case the specification provides only written description for a peptide consisting of SEQ ID NO:3 and a peptide encoded by the amino acid sequence of EBAF of the instant specification and comprises SEQ ID No 3.

Therefore, only an isolated peptide consisting of SEQ ID NO: 3, but not the full breadth of the claim meets the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. (See page 1115.) Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

9. Claims 1-26, 28-38 and 40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to method of determining, detection devices that comprise, contraceptives that comprise, and diagnostic tools that comprise ebaf nucleotide splice variant molecules and reagents that are nucleotide molecules that will detect these variants.

The instant specification discloses the nucleotide sequence for ebaf, and "lefty" which is encoded by a sequence that share 77% sequence identity and 83% sequence similarity to ebaf, but a representative number of nucleotide sequences that would serve as detection reagents that could be used in methods, incorporated into devices, or diagnostic kits and are considered to be ebaf splice variants are described in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application.

Variant sequences of ebaf, would differ from ebaf in ways that are not defined by known molecules that share sequence similarity have not been described. None of these sequences meets the written description provision of 35 U.S.C. 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. (See page 1115.) Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

10. Claims 1-26,27, 28, 40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the utilization of serum and endometrial samples and antisera that specifically bind to EBAF for determining the presence or absence of EBAF in does not reasonably provide enablement for the determination of EBAF or variants thereof in any sample of tissue, or bodily fluid such as brain tissue, saliva, and fecal samples for the determination of fertility or infertility . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant specification teaches EBAF and ebaf, to share signification sequence identity and similarity with other members of the TGF-beta superfamily (see page 3, lines 1-24). The specification also teaches immunoreactivity of antisera to EBAF that reacts with protein species of various sizes (see page 12, lines 1-9).

While the specification clearly teaches specific reagents, the analysis of endometrial tissue, endometrium tissue extracts and serum samples, the specification does not teach the expression of

ebaf in tissues that are not associated with fertility and infertility (reproductive tissues) and serum samples.

Antisera to SEQ ID No 3 (a 16 amino acid peptide) is specific to EBAF and would be able to distinguish one member of the TGF-beta superfamily from another and specifically detect the presence or absence of EBAF.

The instant specification has not shown, nor taught that EBAF would be or is expressed in brain tissue, bone tissue, heart tissue, fecal matter, saliva or spinal fluid, to name a few types of sample that could not predictably produce EBAF at a level that would be diagnostic of disease of the endometrium and correlate with fertility or infertility.

None of the claims directed to methods, diagnostic tools, contraceptives, kits and devices recite any specific reagents of any specific binding specificities, of any specific structure and function, to comprise any specific amount of a reagent, nor any specific conditions for the determination of ebaf or EBAF correlated with the preamble of each method, or to have the recited ability to function as a contraceptive or diagnostic tool.

The instantly claimed invention is enabled for a scope of the claimed invention, as any antibody that does not specifically bind to a sequence of amino acids that is specific to EBAF, would not predictably detect or determine the presence of EBAF in a sample in light of the high level of shared amino acids sequences that EBAF has being a member of the TGF-B superfamily of molecules.

A peptide positive control that is any peptide would provide a relative positive control for the amount of protein in a sample, but would not predictably define the presence or absence of EBAF specific peptides in a sample.

The utilization of antibodies to ebaf nucleotide sequences (instant claim 27, ebaf being defined to be mRNA in the claims) have not been described in such a way that Applicant conveyed with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*.

The person of skill in the art would be required to conduct undue experimentation to utilize any tissue or bodily fluid to determine the presence of ebaf, using any antisera or mRNA of any sequence that may be cross-reactive and/or non-specific for ebaf, and in turn correlate any level of binding with the presence or absence of fertility or infertility, as not specific guidance or teaching has been provided on how to interpret any level of response can be used to determine fertility or infertility when an ebaf non-specific reagent is used. No examples are provided that contain the missing information. The claimed invention is enable for a scope of what is now claimed.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3, 18-26 and 30 are directed to various methods that recite steps in the passive voice. The methods would be made clearly by amending the claims to recite active voice methods steps.

Claims 1-3 recite the phrase "by screening". A sample has not been provided and the screening results have not been compared with any reference sample or negative control. How can diagnosis of irregularities be achieved when a normal level is not defined? How can any level of ebaf be indicative of irregularities? As ebaf is a member of the TGF-beta superfamily what is the ebaf specific reagent used to detect ebaf (TGFbeta-4) in light of the gene sharing conserved sequence with other members of the superfamily? What type of reagent does the term "by" imply? How are the nucleotide sequence of splice variants detected with antibodies in Western blotting which detect proteins? The terms "ebaf" and "ebaf variant" refer to nucleotide sequences as the abbreviations are not capitalized and therefore refer to the coding sequence for the corresponding protein. What antibodies bind selectively to the coding sequence of ebaf? Clarification of the methods steps and reagents used is requested.

Claim 1 recites the term "ebaf". The utilization of abbreviations in the claims is permitted in the claims upon definition of the term at its first appearance in the claims. Is this term intended to refer to a nucleotide sequence or a protein?

Claim 2 depends from claim 1 which recites "ebaf" and defines the screening step to further comprise either a Northern blot or a Western blot. As Northern blot and Western blot methods utilize and detect different biological materials, and the method of claim 1 is directed to the screening for nuclear material, how can a Western Blot be used to detect the nucleotides of claim 1? What is that antibody that is used in the Western blot to detect the nucleotide coding sequence? What is the sample being analyzed?

Claim 3 recites the phrase "further includes immunohistochemical staining". What is the sample? What antibodies are used? What is being immunohistochemically stained in light of the sample being a bodily fluid? What component in the fluid would be stained? Where did the sample originate from so it would be indicative of endometrial irregularities? How can say a cerebral spinal fluid sample be so analyzed to determine information that is indicative of endometrial irregularities?

Claim 4 is directed to a "screening means". What is the structure and/or function of a screening means that would screen a sample for the presence or ebaf? Is the means a machine that would read an calorimetric indicator used in an assay method?

Claim 5 defines the "screening means" to be a Northern blot analysis. Is the means all of the reagents used in a Northern blot? Do the means include all or a portion of the reagents used in a Northern blot? Does the means need only be a single component of a Northern blot analysis, such as a buffer? If this is the case, the claimed invention is not distinctly claimed.

Claim 6 defines the "screening means" to be a Western blot analysis. Is the means all of the reagents used in a Western blot? Do the means include all or a portion of the reagents used in a Western blot? Does the means need only be a single component of the analysis system, such as a buffer, a dye or a gel matrix ? If this is the case, the claimed invention is not distinctly claimed.

Claim 7 recites the phrase "screening means is an immunohistochemical stain". What is being claimed that will selectively stain and detect endometrial irregularities? What is the antibody? What is the stain? Is the stain associated with the antibody or is a secondary label, such as an anti-antibody with a label? Clarification of what the tool is, is requested.

Claim 8 recites the phrase "ebaf protein". As "ebaf" refers to a coding nucleotide sequence, what is an ebaf protein? Is there a protein molecule associated with the nucleotide sequence that is being claimed? What is the protein being detected? Is it EBAF protein?

Claim 9 recites the phrase "wherein the mRNA encoding ebaf is detected" and depends from claim 4. As claim 4 does not recite a detect step, but only a screening means, the "wherein" clause is unclear as to what is being claimed through reciting a methods step to define a tool. What is the tool? What is being used to detect the mRNA? What is the sequence? What is the means? The phrase "the mRNA" lacks antecedent basis in claim 4 from which it depends.

Claims 10-12 recite "wherein" clauses that define specific diseases that are diagnosed. What are the tools being claimed that will be used to diagnose these diseases? No specific tools are recited in the claims. Clarification of what is intended to be the tool, in light of the recitation

of a disease being recited without any biological reagent with any specific structure or function being defined in the claims is requested.

Claims 13 and 14 are directed to a composition and a device . How do the composition and the device differ from one another in light of the fact that they comprise the same components "ebaf in a pharmaceutically acceptable carrier" .

Claim 15 is directed to "screening means for screening a sample for the presence of ebaf", specifically for timing conception. What is the structure of the means? The means has no function and no structure. What biological structure and function does the word "screening" define? The component or components of the kit are not distinctly claimed.

Claim 16 recite a "wherein" clause that defines "ebaf" to be a protein. How can an abbreviation for a nucleotide coding sequence also be representative of a protein? --a protein encoded by ebaf--. Claim 17 defines the term "ebaf" to be a "mRNA". Clearly "ebaf" can not be both a protein and mRNA at the same time. What components are in the diagnostic kit?

Claim 18 recites the phrase "by down-regulating the expression of ebaf". The method does not administer any type of reagent to a female mammal or a tissue sample of endometrium that would express ebaf. The term "by" does not provide a composition that would be effective in "down-regulating the expression" of anything. The method of claim 18 is incomplete, as essential reagents and methods steps are missing.

Claim 19 is directed to a method for "determining endometrial receptivity". What must the endometrium be receptive of? What will the endometrium receive? What is the tissue sample

or bodily fluid that is evaluated to determine "receptivity"? How can brain tissue be used to be indicative of endometrium receptivity? The method does not provide a sample, and no correlation of any results determined does not correlate with the recited preamble. Clarification of the methods steps and the types of samples analyzed is requested.

Claims 20-23 recite the same method as claim 19, with a different "by determining" phrase. Clarification of the sample, methods steps, reagents used in the method and what level of ebaf must be determined to correlate with the preamble of the claim is requested. With respect to claims 20-21, 23, what is the antibody? What is the antibody binding specificity? With respect to claims 22-23, what is the RNA or DNA used to determine the level of ebaf? What is the structure of the reagent? The phrases "by PCR", "by northern, western or southern blot" do not clearly and distinctly define the reagents used in the methods; what are the reagents used?

Claim 24-26 recite the phrase " determining optimal treatment or treatment response". What is the treatment? What is an "optimal treatment"? How is the treatment achieved? What is a suboptimal treatment? What type of response to a treatment is being determined? What type of sample is being analyzed? Is the sample being obtained from a male or female animal? As no sample source is recited in the claims, what type of samples are the ebaf levels being determined in?

Claim 27 is directed to an "antisera" "to ebaf". As "ebaf" has been defined in the claims to be both mRNA and a protein, what is the antisera specific to? Do the antibodies bind to mRNA? What portion of the protein are the antibodies specific to? What is the source of the antisera?

Claims 28-29 are directed to "a marker" for receptivity and infertility, both being defined to be ebaf. How can the one molecule be indicative of both receptivity and infertility at the same time? How are the marker levels distinguished one from the other? The marker comprises ebaf, what other components are present in the marker together with ebaf? Is the marker ebaf or is the marker ebaf in association with another molecule? Clarification of what components make up the marker in addition to ebaf is requested.

Claim 30 recites the phrase "by modulating". What is the substance that modulates the amount of ebaf produced? Is the substance a female hormone? How can ebaf be modulated if a substance is not administered to an animal that produces ebaf?

Claim 31 is directed to a "immunohistology test" . What are the reagents contained in the test? What is the specificity of the immunohistology reagent? Does the immunohistology reagent specifically to a marker indicative of ebaf expression or does it specifically bind to ebaf or EBAF?

Claim 32 recites the phrase "further includes antisera" and depends from claim 31. If claim 32 has an antisera in the kit, what does claim 31 have in it? Does claim 31 comprise an antisera? How can an immunohistology test not comprise an antisera? Claim 32 adds confusion to claim 31 from which it depends, in light of claim 32 set forth that it "further includes antisera", thus defining claim 31 not to include an antisera. Clarification is requested.

Claim 33 is directed to a kit for an "immunoassay". As kits need not comprise all of the reagents needed in an immunoassay, what do the kits comprise? What are the reagents contained in the kit? As claim 34 depends from claim 33 and defines the kit to "further include antisera and

peptides as positive controls", what reagents are present in the kit of claim 33? The invention of claim 33 is not distinctly claimed, in light of claim 34 depending from 33 and defining the absence of antisera in the kit of claim 33.

Claims 34 and 36 recite the phrase "antisera and peptides as positive controls". What is the binding specificity of the antisera? What is the structure and function of the peptides? How can any peptide function as a positive control?

Claim 35 recites the phrase "blotting test". What type of blotting test is being included in the kit? What are the reagents in the kit? Does the kit include paper towels, known to be used in southern blots? Clarification of what reagents and components are in the kit is requested.

Claim 37-38 are directed to kits comprising "a PCR". What is the PCR? What reagents are in the kit? Claim 38 comprises one or more probes, what does claim 37 comprise that will detect ebaf? What is the sequence of the probe or probes that are specific for ebaf in light of the coding sequence sharing 83% sequence similarity with "lefty" (see page 3, lines 17-24)? Is the method intended to detect "lefty" as well as "ebaf"? If this is the case, the invention is not distinctly claimed.

Claim 40 is directed to a device for the detection of at least one variant of ebaf. What is the variant? How does the variant differ from ebaf? What is the reagent which will detect the variant in the molecule, that is NOT ebaf? What is the structure and function of the reagent that has been included in a device? Clarification is requested.

Claim Rejections - 35 U.S.C. § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

14. Claims 1-5, 9-14, 18-19, 22-26, 28-29,35, 37, 39-40 are rejected under 35 U.S.C. 102(a) as being anticipated by Kothapalli et al (May 1997; different inventive entity).

w/d Declaration

The claimed invention is directed to a method of diagnosing endometrial irregularities by screening an endometrial sample of bodily fluid for the presence of ebaf.

(Instant claims 1-5,9, 10-12) Kothapalli et al disclose a method of diagnosing endometrial irregularities by screening an endometrial sample of bodily fluid for the presence of ebaf (see Figure 3, page 2345 and page 2346, col. 2, paragraph 2) using a diagnostic tool (a Northern blot, Figure 1).

(Instant claims 4-5, 15, 17, 35, 37) At page 2343, Methods, the reference discloses a differential display kit for the visualization of RNA (see col. 1, paragraph 2), as well as other kits for the visualization of nucleic acid detection).

(Instant claims 13-14) The composition used in the method, and the diagnostic tool comprise an complementary cDNA molecule that hybridized to the 3' terminal of ebaf or to the entire coding sequence of ebaf (see narrative of Figure 1, page 2344). This composition could be used as a contraceptive composition.

(Instant claims 18-19, 22-26, 28-29(intracellular mRNA in tissue fluids) Northern blotting of tissue aided in the detection of abnormal levels of ebaf (see Figure 1, 2, 3, Table 1, and Figure 4). Both (see page 2343, col. 2, last paragraph) sense (see page 2346, col. 2, paragraph 3) and anti-sense mRNA were disclosed (see Figure 4, page 2346) and used in Northern blot analysis and hybridization of endometrium tissue (antisense).

(Instant claim 30) Differential display of ebaf was shown in a method where the expression of ebaf differed from menstrual cycle phase to another (see page 2345, col. 2, whole paragraph). The modulation of the expression and the effect on fertility was modulated by the human body. As no specific modulating agent or source of modulation is recited in the claims, and the method recites the step of "by modulation" which reads on natural modulation of expression through the various

phases of menstrual cycle, the reference teaches a methods that shows modulation of ebaf that effects fertility.

(Instant claim 39) Figure 6, shows a peptide that comprises SEQ ID No 3 (see C-terminal amino acid sequence).

(Instant claim 40) Northern blots define a device for the determination of "at least one variant of ebaf", wherein "lefty" is disclosed and shown to share significant sequence identity with that of ebaf (see Figure 6) and the cDNA primer set shown on page 2348, col. 1-2, would be able to detect this variant of ebaf. The reference also discloses "lefty" mRNA was isolated upon expression in a mouse embryo that was detected (see page 2349, col. 1, paragraph 2).

The reference anticipates the instantly claimed invention.

15. Claims 4-12, 13-17,20-21, 27-29, 31-38, 40 are rejected under 35 U.S.C. 102(e) as being anticipated by Tabibzadeh (US Pat. 6,294,662 (continuation of '751, priority back to August 1996') or US Pat. 5,916,751).

The claimed invention is directed to kits, diagnostic tools, antisera to EBAF protein, markers in a bodily fluid, a detection device for ebaf and a method of immunohistology.

Tabibzadeh (US Pat. 6,294,662) disclose kits (see '662 col. 11, lines 5; col. 6, line 9; col. 9, line 61), diagnostic tools (see '662 col. 5, lines 18-40), antisera to EBAF protein (see '662 col.

9, III. Immunoassay through to col. 12, line 5), markers in a bodily fluid (see '662 Table 1, col. 6, and col. 6, lines 64-67, cancer tissue expression; col. 5, lines 1-5),a detection device for ebaf (see all figures, Northern Blot) and a method of immunohistology (see '662 col. 10, lines 17-39).

The reference anticipates the instantly claimed invention.

Conclusion

16. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

17. Feinberg et al (US Pat. 5,395,825 and 5,693,479) are cited to show TGF-B associated with fertility and infertility of a mammal.

18.Keck et al (US Pat. 6,040,431) is cited to show an amino acid sequence of TGF-B4 (see SEQ ID No 4).

19. Lee et al (US Pat. 6,428,966) is cited to show Lefty-1, growth differentiation factor.

20.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp
September 7, 2002

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600